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Precision Medicine in Pancreatic Disease—Knowledge Gaps and Research Opportunities:

Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop

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Abstract

A workshop on research gaps and opportunities for Precision Medicine in Pancreatic Disease was sponsored by the National Institute of Diabetes and Digestive Kidney Diseases on July 24, 2019, in Pittsburgh. The workshop included an overview lecture on precision medicine in cancer and 4 sessions: (1) general considerations for the application of bioinformatics and artificial intelligence; (2) omics, the combination of risk factors and biomarkers; (3) precision imaging; and (4) gaps, barriers, and needs to move from precision to personalized medicine for pancreatic disease. Current precision medicine approaches and tools were reviewed, and participants identified knowledge gaps and research needs that hinder bringing precision medicine to pancreatic diseases. Most critical were (*a*) multicenter efforts to collect large-scale patient data sets from multiple data streams in the context of environmental and social factors; (*b*) new information systems that can collect, annotate, and quantify data to inform disease mechanisms; (*c*) novel prospective clinical trial designs to test and improve therapies; and (*d*) a framework for measuring and assessing the value of proposed approaches to the health care system. With these advances, precision medicine can identify patients early in the course of their pancreatic disease and prevent progression to chronic or fatal illness.

Keywords

chronic pancreatitis; consensus workshop; pancreatic cancer; personalized medicine

Pancreatic diseases, including acute pancreatitis, recurrent acute pancreatitis, chronic pancreatitis (CP), pancreatitis-associated diabetes mellitus, pancreatic cancer, and associated syndromes of organ dysfunction or failure, are complex and require a precision medicine approach. Precision medicine is a term that means many things but at its core implies that physicians use an understanding of the mechanisms underlying specific signs and symptoms of disease to focus therapies at highly specific and effective targets.

Precision medicine for pancreatic cancer is a challenging field. On the one hand, genetic testing is being developed to assess the patient's tumor to help in the diagnosis of disease and choice of treatment.[1,2] On the other hand, genetics is also used to classify patients into risk categories before cancer develops to assist in surveillance with various biomarkers.[3–5] Studies are needed to identify risk factors that ascertain high-risk patients and then select appropriate biomarkers and imaging approaches to detect, diagnose, stage, and target treatment of early pancreatic cancers.

Precision medicine for inflammatory disease of the pancreas has made major advances in the past few years. First, a new definition of CP has been adopted that facilitates precision medicine approaches to early detection and management of a progressive group of disorders.[6] Second, consensus has been reached that it is impossible to diagnose *early CP* because the biomarkers are nonspecific and CP *requires* irreversible organ damage.[7,8] Third, in contrasting and comparing the approaches of modern Western medicine to precision medicine, it becomes clear that precision medicine for complex disorders focuses on detecting mechanistic dysfunction and disorders at the cellular and systems level in symptomatic patients, well in advance of disease, and providing a target for therapy.[9] Linking known risk and etiologies to mechanism and clinical signs and symptoms is now possible.[10,11] Both a *top-down* approach (using well-defined populations to correlate specific diseases or disease features with an agnostic collection of genetic and omics data) and a *bottom-up* approach (correlating knowledge of cellular and biological systems with specific disease-associated genetic and omic variants to gain insights into disease mechanisms and to generate predictive models to aid the development of target-specific interventions) must occur together to merge clinical insights with disease mechanisms in each individual patient to achieve personalized medicine.

The purpose of the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) Workshop on Precision Medicine in Pancreatic Disease was to understand the current status of methods and applications of precision medicine to the diagnosis and management of pancreatic disease and to explore approaches to translate information gained through precision medicine to create strategies for personalized approaches for the prevention, early diagnosis, and treatment options for patients with benign or malignant pancreatic disease. Each session and lecture provided insights into the methods of precision medicine and on how to apply them to pancreatic disease as well as guided discussion to

identify the knowledge gaps, barriers, and priorities for conducting basic and clinical studies to advance the field.

PRECISION MEDICINE: LESSONS FROM CANCER

Cancer treatments have improved dramatically in recent years, in part because new measurement technologies have been deployed to identify aspects of cancer that can be manipulated to achieve cancer control. The use of efficient nucleic acid and protein profiling tools has been especially useful to discover recurrently aberrant genes and molecular pathways intrinsic to cancer cells that can be targeted therapeutically. The spectrum of targetable abnormalities varies substantially between tumors, so the administration of targeted drugs must be coupled with rapid inexpensive diagnostics that can identify tumors likely to respond to specific targeted therapies. This is the essence of precision medicine that has led to tumor control or cure for many patients with early-stage disease.

These same drugs also demonstrate efficacy in advanced disease, but control typically is not durable. Recent efforts to improve control have included manipulation of the diverse microenvironments in which disseminated tumor cells live. These include efforts to normalize angiogenesis, stromal fibroblasts, extracellular matrix proteins, and reactivation of immune surveillance. Unfortunately, even the best combinations of drugs that target tumor intrinsic and extrinsic processes have not led to durable responses for the majority of patients with metastatic cancer including pancreatic ductal adenocarcinoma.

Our inability to control metastatic disease stems from a still imperfect understanding of the diverse intrinsic and extrinsic mechanisms that enable tumor cells to escape therapeutic control and from the inability to quickly and effectively recognize and counter newly resistant tumor subpopulations as they arise. These attempts to identify additional therapeutic vulnerabilities need to include comprehensive omic and multiscale image analyses of longitudinal tumor biopsies and blood samples taken during the course of treatment.

For example, investigators have analyzed serial tumor biopsies to assess changes in genome composition, protein expression, and cellular composition using multiplex immunohistochemistry and cyclic immunofluorescence as well as focused ion beam scanning electron microscopy to design, monitor, and adjust the therapy of individual patients. The experience of applying these methods in subjects with breast cancer revealed remarkable on-treatment evolution, heterogeneity between and within individual lesions in the same patient, and novel nanoscale biology that must be managed to achieve therapeutic control. This is the essence of personalized medicine.

The result of this effort, the Serial Measurements of Molecular and Architectural Responses to Treatment program at Oregon Health and Science University, is dedicated to the proposition that treatment with biologically motivated multidrug combination strategies that change during the course of treatment as guided by omic and multiscale imaging measurements can achieve durable and tolerable control of even the most advanced cancers

including pancreatic carcinoma.[12] Lessons learned from this approach to treating malignant disease can be applied to progressive inflammatory diseases such as CP as well.

GENERAL CONSIDERATIONS FOR LARGE DATA SETS

A necessary feature of precision medicine is the expectation that large data sets in biomedicine will provide fresh insights into health and disease that will translate into personalized disease prevention and therapies. To reach this state, we must overcome the significant challenges of data analysis, integration, storage, and result interpretation posed by the generation of enormous data sets generated by multiple methods. To make sense of these large data sets, tools are required that can assemble integrated data generated by omics with a knowledge base of known biological mechanisms and networks to extract and identify significant changes in molecular profiles, construct models of interacting biological networks, map perturbations to causal pathways, construct simulations to predict phenotype, and validate potential biomarkers and therapies. These tools will come from bioinformatics, artificial intelligence (AI), and machine learning. Their role in precision medicine for pancreatic disease was discussed in this session.

Bioinformatics Approaches to Precision Diagnosis

Precision diagnosis is the effort to accurately and precisely determine the etiology of a patient's disease, often to guide treatment. For this reason, precision diagnosis of a patient is a critical component of precision medicine.[13] Bioinformatics is often a critical component of diagnostic development programs.

Several bioinformatics algorithms and approaches are used to develop precision diagnostics, but the field has not converged to a single approach. In some cases, precision diagnosis might require considering and weighing several different lines of information together. Machine learning algorithms are of high interest because they are able to recognize patterns in complex data, enabling better diagnosis of disease. However, machine learning methods are often black box and unable to give clear insight or explanation of their predictions. The role of black box methods in health care remains an open question.[14] If the goal is to understand a disease's subtypes, noninterpretable methods may be less desirable. On the other hand, if improving outcomes is most important, black box methods can sometimes perform better than interpretable methods. The precise trade-offs between different approaches are usually problem specific. The decisions may not lend them-selves to answers that apply in every context. For this reason, careful attention should be paid to defining the precise problems being addressed by bioinformatics analysis so appropriate methods can be used.

The focus of genetics is on the underlying mechanistic disorders, but an additional area of need is biomarkers of disease location, subtype, activity, stage, and response to treatment. Linking image analysis with disease mechanisms provides great opportunities for the future. Deep learning, a recent advance in machine learning, can analyze images with surprising accuracy, providing quantitative and qualitative data to support clinical decisions.[15] Likewise, a patient's disease can be distinct for many reasons, and distinct drug exposure of patients is an important variable. For several reasons, patients can be prescribed drugs

incidentally to the primary diagnosis of importance. Incidentally prescribed drugs can influence the trajectory of diseases, suggesting uses for drugs and mechanistic insight into diseases. For example, epidemiological studies showed that metformin reduced cancer risk in many patients,[16] and it is now being studied as an adjuvant therapy in several cancers.[17] Similar repurposing opportunities might be identified by studying incidentally prescribed medications in patients with pancreatic diseases.

In all cases, systematic collection of patient outcome data is critically important. For example, more data can be collected in a clinical study than can practically be collected in standard clinical practice. From these data, bioinformatics algorithms can be used to identifying specific biomarkers associated with response to different treatments. After identification of putative biomarkers, a focused laboratory test can be developed to direct treatment. Other approaches are also possible, but prospective studies like this may be a key step toward developing precision diagnostics in complex disease. The Kidney Precision Medicine Project (https://kpmp.org/) may be an important investigative model to learn from and adapt for pancreatic disease. Regardless of the adopted strategy, efforts to design prospective studies and to address the concerns arising from scientific, clinical, statistical, and machine learning applications will require interdisciplinary teams.

The Application of AI and Deep Learning in Pancreatic Imaging

Automated analysis of the pancreas in radiological imaging has been historically difficult because of the large shape and size variations among patients and low tissue contrast to surrounding anatomical structures. Recent advances in the machine-learning based analysis of the pancreas in computed tomography (CT) and magnetic resonance imaging (MRI) are changing the landscape of automated analysis of the pancreas. In particular, the advent of deep learning has boosted the practicality of AI in health care and radiological imaging applications. Fully convolutional neural networks have driven the performance of automated segmentation methods and have improved the state-of-the-art significantly.[18–21] Fully convolutional neural networks can now process full 3-dimensional (3D) radiological images including the whole pancreas and produce accurate automatic segmentations in many cases. Accurate and robust automated segmentation results could lead to new clinically relevant applications, potentially reducing miss rates of pancreatic cancers, and improve early detection and screening for pancreatic diseases.[22] For example, segmentations can be useful for further automated analysis, such as the classification of cancerous versus noncancerous pancreatic tissue.[23] Furthermore, pancreas segmentation can be enhanced and combined with multiorgan segmentation models of the major abdominal anatomic regions, typically improving the robustness and accuracy of the segmentation models further.[24,25]

OMICS: THE COMBINATION OF RISK FACTORS AND BIOMARKERS

Until recently, researchers have used omic data sets mainly to derive simple associations between genetic variants and disease phenotypes initially with genome-wide association studies. Advances in high throughput technologies have allowed rapid sequencing of whole genomes and the identification and quantification of biological constituents on unprecedented scales. Rare genetic variants, catalogs of proteins, and metabolites can be

identified in various fluids, cells, and tissues. Protein-to-protein and cell-to-cell interactions can be identified and understood in more detail than ever before. The availability of diverse omics data and tools to analyze cellular pathways allows the discovery of new biological networks and link them to disease pathogenesis. In this section, the role of omics in bringing precision medicine to pancreatic disease was discussed.

Proteomics—A Tool for Cancer Therapeutics

To develop new drugs and therapeutic strategies for diseases associated with genomic alterations such as pancreatic cancer and pancreatitis, it is necessary to go beyond the mere fact of such genomic alterations; instead, it is vital to assess and understand the functional impact of such genomic alterations to identify the key disease drivers and mechanisms that shape tissue heterogeneity. Proteins are the functioning units in a cell, encoded by the genome. Thus, proteomics is the obvious choice to connect genomic alteration and function —a notion underscored by the fact that proteins are the direct targets of most drugs currently in use.

The importance of proteomics to understand the functional ramifications of mutations in proteins became clear when the data from a large-scale quantitative proteomic and transcriptomic study on 50 different colorectal cancer cell lines were analyzed in detail.[26] With over 12,000 proteins identified in total and with more than 8000 proteins identified in more than 80% of the samples, solid conclusions can be drawn: (1) proteomics shows more and tighter modularity than transcriptomics, and (2) loss of function mutations resulted in significantly more changes of the proteome than the transcriptome.[27] These findings highlight the need to go beyond DNA and RNA sequencing to understand the role of genomic alterations.

Given the importance of proteomics and its complementarity to genomics or transcriptomics, major advances are currently being made.[28] We expect that in the near future 4000 proteins can easily be identified in a single tissue specimen within 30 minutes of instrument time. At such throughput, routine proteomic analyses of clinical tissue and tumor specimens will become a viable option accelerating the realization of personalized medicine.

Genomics—A Tool for Therapeutics Development in Benign Pancreatic Disease

It is unlikely that a single omics technology will be sufficient to significantly alter the drug development process. Instead, the processes have to be assessed from various different angles including genomics.[29] Although genetic mutations are often neither sufficient nor necessary for a particular disease, knowing the exact map of genetic mutations in the context of a disease such as pancreatitis[30] will play a major role in improving the stratification of the patients, which will be essential for tackling the problem of massive attrition during today's drug development: about 90% of all drug candidates fail, especially during phase II, owing to toxicity or a lack of efficacy.

Such attrition rate in the development of drugs will be an impediment for personalized medicine and individualized therapies. Thus, improving the drug development process will be a prerequisite to realize precision medicine. To fulfill the mission of precision medicine,

modern genomics tools will have to be used to provide deeper understanding of the genetic basis of biological mechanisms and pathways.

These considerations are particularly important in complex disorders such as pancreatitis. For such a disease, it is expected that genomic analysis will identify hundreds of genetic variants that contribute to disease risk, progression, and severity.[31] However, because effect sizes of the different variants on the traits will be small, it is expected that the disease is the result of changes in gene expression rather than changes in the protein sequence, which underscores the notion of the need for a system biological approach to combine genomics, transcriptomics, and proteomics. Therefore, thorough genomic evaluation will have to be coupled with deep molecular and clinical phenotypic data to enable the development of genotype-phenotype response curves, which will be a critical element in validating therapeutic hypotheses and moving us closer to precision medicine.

Novel Tumor-Stromal Metabolic Reprogramming—Metabolomics as a Tool to Understand Tumor Biology and Identify Actionable Therapeutic Targets

The tumor microenvironment is composed of complex interactions among malignant, immune, endothelial, and stromal cells. Recent technological advances in mass cytometry, single-cell RNA sequencing, and highly multiplexed in-situ imaging are providing a deeper characterization of the tumor microenvironment.[32] In addition, novel computational techniques that enable cell-specific deconvolution have been applied to bulk gene expression data sets to produce a pan-cancer cellular decomposition of the tumor microenvironment. Although the composition of the tumor microenvironment is being better characterized, more progress is needed to reconstruct functional interactions between cell types comprising the tumor microenvironment. Integrative experimental and computational approaches that combine imaging, genomic, and proteomic data to characterize the tumor microenvironment are revealing novel mechanisms of tumor-stromal metabolic programming that are critical to tumor progression and drug response.

An example of this approach has identified new molecular processes associated with tumor metabolism from the integrative analysis of imaging and genomic data of human non–small cell lung cancer (NSCLC).[33,34] An analysis of the transcriptome of bulk and flow-sorted human primary NSCLC together with ^{18}F-fluordeoxyglucose-positron emission tomography scans provides a clinical measure of glucose uptake. Tumors with higher glucose uptake were functionally enriched for molecular processes associated with invasion in adenocarcinoma and cell growth in squamous cell carcinoma. Moreover, genes were identified that correlated to glucose uptake that were predominately overexpressed in a single cell-type comprising the tumor microenvironment. Most of these genes were expressed by malignant cells in squamous cell carcinoma, whereas in adenocarcinoma, they were predominately expressed by stromal cells, particularly cancer-associated fibroblasts. Among these adenocarcinoma genes correlated to glucose uptake, glutamine-fructose-6-phosphate transaminase 2 (*GFPT2*), which codes for the glutamine-fructose-6-phosphate aminotransferase 2 (*GFAT2*), a rate-limiting enzyme of the hexosamine biosynthesis pathway, is responsible for glycosylation. Expression of *GFPT2* was predictive of glucose uptake independent of *GLUT1*, the primary glucose transporter, and was prognostically

significant at both gene and protein level. Normal fibroblasts transform to cancer-associated fibroblast–like cells, after transforming growth factor β treatment, and upregulate hexosamine biosynthesis pathway genes, including *GFPT2*. These studies provide new evidence of histologically specific tumor stromal properties associated with glucose uptake in NSCLC and identify GFPT2 as a critical regulator of tumor metabolic reprogramming in adenocarcinoma. In ongoing work, GFPT2-expression is associated with CT features of tumor progression in NSCLC. High-dimensional phenotypic malignant cell states induced by stromal-derived factors have been characterized,[35] and these states demonstrate expressions for differential drug sensitivity. This work provides new compelling evidence of tumor-stromal metabolic reprogramming, which contributes to tumor progression and may inform drug selections and therapeutic responses. Similar approaches are now being applied to pancreatic adenocarcinoma.

Multiplex Explorations of Inflammation in Cancer and Pancreatitis

One of the major challenges in studying benign and malignant pancreatic disease has been tissue access. This has hampered not only investigation of disease pathogenesis but also ways to monitor and follow disease course. In inflammatory bowel disease for example, endoscopic guided tissue sampling has allowed for progress in assessing disease state and using stringent metrics to define disease activity and remission. As a result, simultaneous access to disease site and cells in circulation has allowed the study of vast numbers immune cells and signals using flow-based mass cytometer or cytometry time-of-flight.[36] The findings from this study offer ways to decipher disease heterogeneity, response to therapy, and future blood-based cellular assays to classify and monitor patients with high degree of precision noninvasively. Such tools are now being applied in experimental pancreas disease models to study disease induction, recovery, and progression from acute to chronic inflammatory states. With the support of NIDDK and National Cancer Institute sponsored Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, an in-depth study to investigate circulating immune cells in patients with different forms of pancreatitis and associated diabetes is underway. Investigators are also obtaining human pancreata from deceased organ donors and from patients with refractory CP undergoing total pancreatectomy and islet autotransplantation for studies of the various cell types in the pancreas.[37]

Flow-based assays used for any omics studies rely on isolating cells from their natural and/or existing environment; thus, complementary omics-based imaging studies are necessary to determine not only geographic but also functional localization of cells. Many imaging studies that allow for detecting over 30 to 60 antigens and that depend on assays such as mass cytometry, chemical quenching, or in situ polymerization-based indexing procedures have been developed in the past few years.[38–40] Such technologies provide a closer look at in situ cellular interactions and have a higher likelihood of developing targeted therapies and are now being used to study benign and malignant pancreatic diseases.

PRECISION IMAGING: FROM MACRO TO MICRO

Over the past 5 years, the technologies to image a broad range of biologic molecules and tissue structures in vivo and in tissue samples has dramatically advanced. With these advances has come the need to standardize tissue preparations as well as the assays of function and content and to develop algorithms that can integrate a broad range of data inputs. To make these data broadly accessible and maximize the extraction of information, AI is being used to discover novel relationships, and new methods of dynamic data display are being developed. These advances are being used to tissues in vivo, excised normal and diseased tissues, and tissue sections. This session reviewed new approaches ranging from whole body imaging to integrated 3D localizations of multiple molecules in tissue fragments and discussed how they aid precision medicine for pancreatic disease.

Quantitative Imaging of CP

One of challenges in clinical pancreatology has been the assessment of the presence and severity of CP. A central histopathological feature of this disease is fibrosis. The precise role of fibrosis in the development of other disease features such as loss of endocrine and exocrine cell mass and function, pain development, and enhanced cancer risk remains unclear. This lack of knowledge is very much a reflection of our inability to assess pancreatic fibrosis with noninvasive or minimally invasive technologies, particularly in early stages. Recently, significant efforts have been made to incorporate parenchymal changes seen with MRI to complement the ductal changes in identifying CP. The extracellular matrix can broadly affect tissue function by multiple mechanisms including cell signaling by soluble ligands, signaling through mechanotransducers, and vascular compression.

Prior studies have shown that the magnetic resonance (MR) T_1 signal decreases in CP, which can be objectively quantified using T_1 mapping, correlated with pancreatic exocrine dysfunction.[41,42] Extracellular volume (ECV) imaging is a quantitative MR method that exploits changes to the extracellular matrix and can detect fibrosis in patients with CP. Magnetic resonance elastography, which has been successfully used to evaluate hepatic fibrosis by assessing tissue stiffness, is now being adapted for assessment of pancreatic fibrosis.[43] Fibrosis and acinar cell loss can also be quantitatively assessed by estimating the ECV fraction with gadolinium-enhanced MRI.[44] Finally, MR cholangiopancreatography, in conjunction with stimulation of the pancreas by secretin, has been used to assay pancreatic secretory responses by quantitative assessment of fluid secreted into the gut lumen and for simultaneous assessment of duct morphology and compliance.[45] There is need for a quantitative scoring system as a biomarker for CP. Such a scoring system is the focus of the MINIMAP study (MRI as a noninvasive method for the assessment of pancreatic fibrosis), which is funded by NIDDK.

Advances in Molecular Imaging

There is also an impetus for developing new molecular imaging reagents because the use of MRI and CT has not imparted long-term benefits to pancreatic cancer patients.[46] The shortcomings may be owing to the inability of these modalities to detect early neoplasms or identify potential therapeutic targets. Optimal targets would be specific, disease related, in

sufficient density to be easily detected, and expressed on the cell surface. Potential ligands include antibodies, nanoparticles, proteins, and peptides.[47] An example of a potential target is the intracellular scaffolding protein plectin that redistributes to a cell surface on pancreatic cancer cell and other types of cancer cells.[48] In addition, the protein can be used selectively as a target for anticancer agents.[49]

Next-Generation MALDI IMS: Enabling Molecular Microscopy in the New Age of Biology and Medicine

The application of matrix-assisted laser-desorption/ionization (MALDI) imaging mass spectrometry (IMS) to detect biologic and pharmacologic substances in tissue sections is an important adjunct to precision medicine.[50] Peptides, proteins, carbohydrates, lipids, oligonucleotides, and pharmacologic agents and their metabolites can be imaged by MALDI IMS. It can be used with frozen or fixed tissues, although detection of lipids can be compromised by tissue processing. Resolution of the technique is at the cellular level (about 10 μm), and 2D and 3D reconstructed images can be generated. A great potential advance for IMS is the potential for merging data images from this technique with other forms of imaging such as autofluorescence and immunolabeling.[51] Advanced computational processing also has the potential to merge a low-resolution image in one modality with a high-resolution image from another modality to produce a high-resolution image of both data sets. Finally, high-resolution immunology labeling of biologic specimens can be obtained by labeling antibodies with select heavy metals that can be detected by IMS. Over a dozen antibodies can be simultaneously imaged on the same specific using this technique.

Application of Machine Learning and Mass Spectrometry Imaging to Malignancy

Machine learning platforms can analyze and combine a range of data sets into 2D and 3D images that can be manipulated to show varied associations such as the relationships with a cancer cell and a metabolic product or a drug.[52] Algorithms have been developed to discover new cancer networks and combined with structural and pharmacologic drug information to identify new therapeutic agents.[53] This methodology integrates analytic tissue data with clinical information while recognizing the challenges presented by using distinct sources with varied nomenclature.[54]

GAPS, BARRIERS, NEEDS, AND HOW TO GET FROM PRECISION MEDICINE TO PERSONALIZED MEDICINE FOR PANCREATIC DISEASE

There remain multiple challenges in moving to personalized medicine approaches in pancreatitis and pancreatic cancer. This conference has reviewed some of the multiple opportunities and challenges in transitioning from nonspecific therapies to individually targeted therapies. This section focuses on some novel approaches and an overview of the gaps, barriers, and research needed to facilitate progress toward personalized medicine in pancreatic diseases.

Translating Regulatory Network-Based Personalized Medicine for Pancreatic Cancer

Personalizing treatment, by identifying individual patient characteristics or tumor types, is increasingly becoming the standard clinical practice for cancer in general. Treatment has transitioned from nonspecific therapies directed toward proliferating cells to targeted therapies specific to the tumor susceptibility of each patient. However, in the case of pancreatic cancer, improvements in patient outcomes have been incremental. Personalized medicine approaches in pancreatic cancer are the culmination of decades of investment in understanding the molecular responses of tumor cells to targeted interventions. To date, personalized medicine paradigms have largely focused on genomic alterations encoded in tumor genomes, using a fairly limited set of therapeutic tools that are known or theorized to have selective efficacy in a tumor-specific genetic context. When successful, this approach can be extremely effective, as evidenced by several high-profile successes such as checkpoint blockade inhibitors for rare microsatellite-high pancreatic cancers. Unfortunately, the majority of tumor genes lack such *actionable* alterations or their alterations frequently fail to respond to targeted interventions or relapse quickly. Thus, context matters, which is challenging to define and then target. One approach to consider is to evaluate RNA expression rather than DNA content of the tumor.

RNA expression serves as a sensitive snapshot of cellular regulatory states.[55] However, challenges in systematically interpreting RNA expression profiles have constrained their practical use for precision or personalized medicine. Regulatory network analysis is a systems biology approach that addresses these challenges and forms the basis for an RNA-guided personalized medicine paradigm that identifies master transcriptional regulators that are hyperactivated or hyperrepressed in a patient's tumor and matches them to drugs that invert their activity.[56] For example, a pancreatic cancer implementation model has been developed using this approach. The model has received Clinical Laboratory Improvement Amendments certification, making it more likely to be available for clinical use. The technology has led to the launching of a phase Ib clinical trial for metastatic pancreatic cancer patients. Moreover, application of regulatory network techniques to bulk tissue, laser capture microdissection, and single cell expression profiles has enabled a deeper understanding of the molecular subtypes that comprise this disease and their association with tumor stroma.[57,58] This model represents one promising personalized medicine approach example in pancreatic cancer.

The Need for Deeply Phenotyped Data Sets

Improving the prognosis of pancreatic cancer may lie not only in treatment but also in early detection, enabled by longitudinal deep phenotyping and analysis of routine laboratory tests, genomics, metabolomics, proteomics, microbiomics, and even lifestyle. For example, the Institute for Systems Biology generated a deeply phenotyped longitudinal data set from a real-world population for over 6200 individuals across the wellness to disease spectra who participated in a consumer wellness program between 2015 and 2019 and shared their deidentified data for research purposes.[59,60] For each individual, a personal, dense, dynamic, data (PD3) cloud that included genomics and longitudinal measures of clinical laboratories, metabolomics, proteomics, and gut microbiomics was generated. This also included data from wearable monitors and questionnaires to capture user-reported measures of lifestyle,

physical health, and mental health. These data are supporting new approaches to quantifying wellness and disease states, and influencing our thought process about personalized medicine biomarkers of wellness to disease transition. Analysis of such cohorts can improve our understanding of major unmet needs in precision medicine, specifically in pancreatic diseases.

Preliminary work on atypical value analysis within these PD3 clouds has yielded several promising population-level observations and individualized case studies. Divergence profiles,[61] a bioinformatic approach based on reference populations matched by age, sex, and ethnicity, can be calculated for participants who received a cancer diagnosis while enrolled in the program. These profiles showed consistently extreme values over time in important systems related to general and tissue-specific cancer processes, such as immune system responses for leukemia and β islet cell-specific responses for pancreatic cancer. In the case of a seemingly healthy 60-year-old woman, later diagnosed with stage IV pancreatic cancer, PD3 analysis of the plasma proteome identified 5 of 16 proteins associated with tumor necrosis factor signaling with atypical values 4 months before diagnosis. Five extreme values within a PD3 cloud with thousands of analytes is not surprising. However, finding that these 5 proteins are part of a single network or system becomes highly significant and biologically meaningful. Longitudinally, an atypical increase in the cancer-associated (and pancreas-specific) protein concentrations over the 1.5 years before diagnosis was observed. The most extreme example is the delta-like noncanonical Notch ligand 1, a regulator of cell growth and neuroendocrine differentiation that is expressed in β cells of the adult pancreas. From a systems-based perspective, it was clear that the number of dysregulated pathways, analyzed by a modified version of the Differential Rank Conservation algorithm,[62] increased longitudinally, well before a clinical diagnosis was made in this participant. The Differential Rank Conservation algorithm is an early application of a strategy to develop *metabiomarkers* based on atypical results of properties of known pathways or systems. The pancreas-specific protein that was identified in the blood, along with the divergent manifestation of tumor necrosis factor signaling proteins, may serve as potential early biomarkers for pancreatic cancer detection.[63]

Although still in its early stages, PD3 cloud analysis has demonstrated that deep phenotyping can transform our thinking about diagnostic discovery and, ultimately, ways to deploy personalized therapies into clinical practice. The analysis of deeply phenotyped data sets for real-world populations and characterizations of precancer to postcancer transition dynamics will facilitate the development of new diagnostics, improve our understanding of organ pathology, and advance the field to provide medical interventions for pancreatic diseases. This approach also demonstrates the massive amount of data, which can be collected on individual patients in a personalized medicine paradigm.

Barriers and Research Priorities for Precision Medicine

Although the high-level concepts of precision medicine are becoming clearer, there remain many information, integration, translation, logistic, and acceptance barriers that future, well-designed, basic and clinical research projects will need to sur-mount before personalized medicine becomes a reality for pancreatic diseases.

Barriers to collecting information must be overcome. Precision medicine depends on accurate information about patients' health history, genetics, metabolism, and toxic exposures in the context of other environmental and social factors from many individuals with and without pancreatic disease. At present, much available information is inaccurate or incomplete or difficult to extract from electronic medical records. The technology to accurately collect and store the large amounts of data required by precision medicine is improving, but more refinements are needed.

Genetic information can establish an association with disease, but association does not prove causality. Additional functional studies are required to define the potential pathogenicity of each genetic variant associated with disease. Ideally, the mechanism should be evaluated under strict conditions in appropriate cell or animal models. This mechanistic information must be stored and integrated with genetic, clinical, metabolic or biomarker, environmental, and life-style data to define the complex mechanisms underlying pancreatic diseases. Understanding the mechanism underlying each genetic variant can only be done from the ground-up approach of basic science.

Discoveries of basic science must then be translated into new therapies and clinical practice. Historically, investigators have used randomized controlled trials to determine if new diagnostic tests or therapies are effective in patients with a particular disease. This model is limited in complex heterogenous disorders such as pancreatic disease. Thus, efforts to better subclassify patients and innovative designs for clinical trials are needed to facilitate the identification and translation of new concepts or treatments from the literature to clinical practice.

Even if the barriers listed previously are overcome, the application of precision medicine still faces logistical barriers. Accessing health care data outside of a health system is often difficult, and even if overcome, the data are often incomplete. In addition, the ability to fund large multidisciplinary programs needed to gather and process the information that enables precision medicine is difficult. New processes for reviewing and funding these programs are essential. Once new approaches are identified, regulatory agencies must adapt and accept new criteria for efficacy and innovative models for prospective clinical studies and trials.

Lastly, health systems, payers, providers, and patients must accept the utility of precision medicine. We must demonstrate the value of precision medicine in improving health at a cost and efficiency that are acceptable to all parties. Convincing them will take education and demonstrations of improvements in the health and lives of patients with pancreatic disorders.

SUMMARY OF GAPS, BARRIERS, RESEARCH NEEDS

- Formulating clinical questions and hypotheses to drive the technologies; creating teams of clinicians, biologists, radiologists, and others to translate the massive data into actionable steps and improve diagnostics; and developing therapeutics and preventive methods is a priority.

- Collaboration among institutions to generate and share large data sets, develop tools for analysis, and translate these data into actionable clinical steps including deep learning, machine learning, and AI for pancreatic diseases is essential.
- Multidisciplinary collaboration across expertise is also essential to maximize the value of existing data, specimens, and imaging data.
- Funding support for large teams across multiple areas of expertise and core facilities will be needed to achieve a goal of precision medicine for pancreatic diseases.
- Improved and more widely available advanced instruments, computational tools, and platforms are needed to derive insight from integrated multiomic data and other data streams.
- Information systems that collect, annotate, and quantify and deliver critical pieces of information are required to inform mechanistic and classification models.
- Multi-institutional data repositories for early detection of pancreatic cancer using AI and machine learning are needed.
- New tools to understand the roles of genetics on complex outcomes of pancreatic diseases must be developed.
- Incorporating stroma and cancer-stroma crosstalk into AI analyses is a priority.
- Standardized definition and normal ranges or typical values across thousands of poorly characterized analytes, including the characterization of the importance of confounding variables (sex, age, genetics, body mass index, etc) for each analyte, is required to allow comparisons among different studies.
- Longitudinal profiles of measurements and analytes in individuals, such as the characterization of the personalized trajectories of individuals transitioning into a disease state, are also needed. For diseases that are dynamic (pancreatic cancer undergoing therapy, pediatric pancreatitis), longitudinal studies with careful biomarker collection including immune biomarkers, microbiome, MRI/MR cholangiopancreatography, genomics, epigenetics, and environmental, psychosocial, and socioeconomic factors are a necessary research goal.
- Using omics, multiplex immunostaining, and 3D scanning electron microscopy to study intercellular interactions and the microenvironment and to develop efficacious and nontoxic drugs is an important goal.
- Developing easily measurable biomarkers such as blood biomarkers or anatomic imaging methods with which to design therapies, follow response and resistance to treatment, and avoid toxicity is needed.
- Understanding the impact of the overwhelming volume of minor variants in noncoding regions requires a large volume of patients with ethnic and racial diversity, of all ages, and from varied geography.

- Radiomics including T_1 mapping, ECV, diffuse-weighted imaging, and MR elastography of the pancreas to stage CP across age groups and validation in large cohorts is an important research priority.
- Molecular imaging or MALDI IMS of pancreas samples from humans or animals that mimic human disease to study targets of inflammation, fibrosis, and cancer; identify biomarkers; and develop therapeutics is an essential goal.
- Obtaining pancreas tissues from humans is a major barrier especially early in the disease course. Therefore, it is paramount to share and procure precious healthy and diseased human tissues.
- Tissue access, sharing, and standardization for preservation, processing, and reporting, ideally through Clinical Laboratory Improvement Amendments–approved laboratories for omics, are essential to provide accurate data.
- Developing animal models that more accurately mimic human pancreatic disease is a research priority.
- Prospective clinical studies and trials are needed to determine if the predictions of precision medicine models are accurate and how they can be improved.
- A value assessment framework to demonstrate and quantify for institutions and payers the benefit from each dollar that is spent on health care in a precision medicine model for health systems, payers, providers, and patients is needed.
- The effects of privacy laws on access to clinical information and materials are a barrier that needs to be addressed.

CONCLUSIONS

Precision medicine has great promise to improve the lives and health of many and to be of value to the health care system. Fortunately, methods to collect, organize, and analyze large data sets and imaging and omic technologies to implement precision medicine are moving forward rapidly. Still, there remain many barriers to implementation of precision medicine for pancreatic disorders. The largest barriers are developing and funding task forces that can obtain the types of information that are critical for understanding biological processes and responses to injury in relevant cells and tissues in the context of genetic and environmental factors. Second, there needs to be the development of information systems that collect, annotate, quantify, and deliver critical pieces of information to inform mechanistic and classification models. Third, there need to be creative prospective clinical trials to determine if the predictions of precision medicine models are accurate and how they can be improved. Finally, there needs to be a valid value assessment framework to demonstrate and quantify for institutions and payers the benefit from each dollar that is spent on health care in a precision medicine model for health systems, payers, and patients.

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REFERENCES

1. Singhi AD, George B, Greenbowe JR, et al. Real-time targeted genome profile analysis of pancreatic ductal adenocarcinomas identifies genetic alterations that might be targeted with existing drugs or used as biomarkers. Gastroenterology. 2019;156:2242–2253.e4. [PubMed: 30836094]
2. Singhi AD, Nikiforova MN, Chennat J, et al. Integrating next-generation sequencing to endoscopic retrograde cholangiopancreatography (ERCP)-obtained biliary specimens improves the detection and management of patients with malignant bile duct strictures. Gut 2019 pii: gutjnl-2018-317817. [Epub ahead of print].
3. Singhi AD, Koay EJ, Chari ST, et al. Early detection of pancreatic cancer: opportunities and challenges. Gastroenterology. 2019;156: 2024–2040. [PubMed: 30721664]
4. Abe T, Blackford AL, Tamura K, et al. Deleterious germline mutations are a risk factor for neoplastic progression among high-risk individuals undergoing pancreatic surveillance. J Clin Oncol 2019;37:1070–1080. [PubMed: 30883245]
5. Stoffel EM, McKernin SE, Brand R, et al. Evaluating susceptibility to pancreatic cancer: ASCO provisional clinical opinion. J Clin Oncol 2019; 37:153–164. [PubMed: 30457921]
6. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. Pancreatology. 2016;16:218–224. [PubMed: 26924663]
7. Whitcomb DC, Shimosegawa T, Chari ST, et al. International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. Pancreatology. 2018;18:516–527.
8. Whitcomb DC. Peering into the “black box” of the complex chronic pancreatitis syndrome. Pancreas 2016;45:1361–1364. [PubMed: 27748718]
9. Whitcomb DC. Primer on precision medicine or complex chronic disorders. Clin Transl Gastroenterol 2019;10:e00067. [PubMed: 31335357]
10. Whitcomb DC. What is personalized medicine and what should it replace? Nat Rev Gastroenterol Hepatol 2012;9:418–424. [PubMed: 22614753]
11. Whitcomb DC, North American Pancreatitis Study Group. Pancreatitis: TIGAR-O version 2 risk/etiology checklist with topic reviews, updates, and use primers. Clin Transl Gastroenterol 2019;10:e00027. [PubMed: 31166201]
12. Mitri ZI, Parmar S, Johnson B, et al. Implementing a comprehensive translational oncology platform: from molecular testing to actionability. J Transl Med 2018;16:358. [PubMed: 30551737]
13. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. N Engl J Med 2012;366:489–491. [PubMed: 22256780]
14. Holm EA. In defense of the black box. Science. 2019;364:26–27. [PubMed: 30948538]
15. Marsh JN, Matlock MK, Kudose S, et al. Deep learning global glomerulosclerosis in transplant kidney frozen sections. IEEE Trans Med Imaging. 2018;37:2718–2728. [PubMed: 29994669]
16. Zhang P, Li H, Tan X, et al. Association of metformin use with cancer incidence and mortality: a meta-analysis. Cancer Epidemiol 2013;37: 207–218. [PubMed: 23352629]
17. Coyle C, Cafferty FH, Vale C, et al. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. Ann Oncol 2016;27: 2184–2195. [PubMed: 27681864]

18. Shelhamer E, Long J, Darrell T. Fully convolutional networks for semantic segmentation. IEEE Trans Pattern Anal Mach Intell 2017;39:640–651. [PubMed: 27244717]
19. Cai J, Lu L, Zhang Z, et al. Pancreas Segmentation in MRI using Graph-Based Decision Fusion on Convolutional Neural Networks. Med Image Comput Comput Assist Interv 2016;9901:442–450. [PubMed: 28083570]
20. Roth HR, Lu L, Lay N, et al. Spatial aggregation of holistically-nested convolutional neural networks for automated pancreas localization and segmentation. Med Image Anal 2018;45:94–107. [PubMed: 29427897]
21. Zhou Y, Xie L, Shen W, et al. A Fixed-Point Model for Pancreas Segmentation in Abdominal CT Scans In: Medical Image Computing and Computer Assisted Intervention—MICCAI 2017. Quebec City, Canada: Springer International Publishing; 2017:693–701.
22. Lugo-Fagundo C, Vogelstein B, Yuille A, et al. Deep learning in radiology: now the real work begins. J Am Coll Radiol 2018;15:364–367. [PubMed: 29290592]
23. Liao WC, Wu T, Liu KL, et al. Differentiation between pancreatic cancer and normal pancreas on computed tomotraphy with artificial intelligence. Gastroenterology. 2019;156(6 suppl 1):S–59 abstract 300.
24. Gibson E, Giganti F, Hu Y, et al. Automatic multi-organ segmentation on abdominal CTwith dense V-networks. IEEE Trans Med Imaging. 2018;37: 1822–1834. [PubMed: 29994628]
25. Wang Y, Zhou Y, Shen W, et al. Abdominal multi-organ segmentation with organ-attention networks and statistical fusion. Med Image Anal 2019;55: 88–102. [PubMed: 31035060]
26. Roumeliotis TI, Williams SP, Gonçalves E, et al. Genomic determinants of protein abundance variation in colorectal cancer cells. Cell Rep 2017;20: 2201–2214. [PubMed: 28854368]
27. Wang J, Ma Z, Carr SA, et al. Proteome profiling outperforms transcriptome profiling for coexpression based gene function prediction. Mol Cell Proteomics. 2017;16:121–134. [PubMed: 27836980]
28. Zhang B, Whiteaker JR, Hoofnagle AN, et al. Clinical potential of mass spectrometry-based proteogenomics. Nat Rev Clin Oncol 2019;16: 256–268. [PubMed: 30487530]
29. Floris M, Olla S, Schlessinger D, et al. Genetic-driven druggable target identification and validation. Trends Genet 2018;34:558–570. [PubMed: 29803319]
30. Mayerle J, Sendler M, Hegyi E, et al. Genetics, cell biology, and pathophysiology of pancreatitis. Gastroenterology. 2019;156: 1951–1968.e1. [PubMed: 30660731]
31. Nelson MR, Tipney H, Painter JL, et al. The support of human genetic evidence for approved drug indications. Nat Genet 2015;47:856–860. [PubMed: 26121088]
32. Gentles AJ, Newman AM, Liu CL, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nat Med 2015;21: 938–945. [PubMed: 26193342]
33. Bakr S, Gevaert O, Echegaray S, et al. A radiogenomic dataset of non-small cell lung cancer. Sci Data. 2018;5:180202. [PubMed: 30325352]
34. Zhang W, Bouchard G, Yu A, et al. *GFPT2*-expressing cancer-associated fibroblasts mediate metabolic reprogramming in human lung adenocarcinoma. Cancer Res 2018;78:3445–3457. [PubMed: 29760045]
35. Karacosta LG, Anchang B, Ignatiadis N, et al. Mapping lung cancer epithelial-mesenchymal transition states and trajectories with single-cell resolution. bioRxiv 2019;570341.
36. Rubin SJS, Bai L, Haileselassie Y, et al. Mass cytometry reveals systemic and local immune signatures that distinguish inflammatory bowel diseases. Nat Commun 2019;10:2686. [PubMed: 31217423]
37. Bellin MD. A role for total pancreatectomy and islet autotransplant in the treatment of chronic pancreatitis. Am J Gastroenterol 2018;113:324–326. [PubMed: 29460919]
38. Angelo M, Bendall SC, Finck R, et al. Multiplexed ion beam imaging of human breast tumors. Nat Med 2014;20:436–442. [PubMed: 24584119]
39. Giesen C, Wang HA, Schapiro D, et al. Highly multiplexed imaging of tumor tissues with subcellular resolution by mass cytometry. Nat Methods. 2014;11:417–422. [PubMed: 24584193]
40. Goltsev Y, Samusik N, Kennedy-Darling J, et al. Deep profiling of mouse splenic architecture with CODEX multiplexed imaging. Cell. 2018;174: 968–981.e15. [PubMed: 30078711]

41. Tirkes T, Fogel EL, Sherman S, et al. Detection of exocrine dysfunction by MRI in patients with early chronic pancreatitis. Abdom Radiol (NY). 2017; 42:544–551. [PubMed: 27660281]
42. Tirkes T, Lin C, Fogel EL, et al. T_1 mapping for diagnosis of mild chronic pancreatitis. J Magn Reson Imaging. 2017;45: 1171–1176. [PubMed: 27519287]
43. Wang M, Gao F, Wang X, et al. Magnetic resonance elastography and T_1 mapping for early diagnosis and classification of chronic pancreatitis. J Magn Reson Imaging. 2018;48:837–845.
44. Tirkes T, Lin C, Cui E, et al. Quantitative MR evaluation of chronic pancreatitis: extracellular volume fraction and MR relaxometry. AJR Am J Roentgenol 2018;210:533–542. [PubMed: 29336598]
45. Sainani NI, Kadiyala V, Mortele K, et al. Evaluation of qualitative magnetic resonance imaging features for diagnosis of chronic pancreatitis. Pancreas 2015;44:1280–1289. [PubMed: 26465953]
46. Kauhanen SP, Komar G, Seppanen MP, et al. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. Ann Surg 2009;250:957–963. [PubMed: 19687736]
47. Srinivasarao M, Galliford CV, Low PS. Principles in the design of ligand-targeted cancer therapeutics and imaging agents. Nat Rev Drug Discov 2015;14:203–219. [PubMed: 25698644]
48. Shin SJ, Smith JA, Rezniczek GA, et al. Unexpected gain of function for the scaffolding protein plectin due to mislocalization in pancreatic cancer. Proc Natl Acad Sci U S A 2013;110:19414–19419. [PubMed: 24218614]
49. Dasa SSK, Diakova G, Suzuki R, et al. Plectin-targeted liposomes enhance the therapeutic efficacy of a PARP inhibitor in the treatment of ovarian cancer. Theranostics. 2018;8:2782–2798. [PubMed: 29774075]
50. Caprioli RM. Imaging mass spectrometry: a perspective. J Biomol Tech 2019;30:7–11. [PubMed: 30918475]
51. Van de Plas R, Yang J, Spraggins J, et al. Image fusion of mass spectrometry and microscopy: a multimodality paradigm for molecular tissue mapping. Nat Methods. 2015;12:366–372. [PubMed: 25707028]
52. Veselkov K, Sleeman J, Claude E, et al. BASIS: high-performance bioinformatics platform for processing of large-scale mass spectrometry imaging data in chemically augmented histology. Sci Rep 2018;8:4053. [PubMed: 29511258]
53. Veselkov K, Gonzalez G, Aljifri S, et al. HyperFoods: machine intelligent mapping of cancer-beating molecules in foods. Sci Rep 2019;9:9237. [PubMed: 31270435]
54. Galea D, Laponogov I, Veselkov K. Exploiting and assessing multi-source data for supervised biomedical named entity recognition. Bioinformatics. 2018;34:2474–2482. [PubMed: 29538614]
55. Califano A, Alvarez MJ. The recurrent architecture of tumour initiation, progression and drug sensitivity. Nat Rev Cancer. 2017;17:116–130. [PubMed: 27977008]
56. Alvarez MJ, Shen Y, Giorgi FM, et al. Functional characterization of somatic mutations in cancer using network-based inference of protein activity. Nat Genet 2016;48:838–847. [PubMed: 27322546]
57. Maurer C, Holmstrom SR, He J, et al. Experimental microdissection enables functional harmonisation of pancreatic cancer subtypes. Gut 2019;68:1034–1043. [PubMed: 30658994]
58. Arnes L, Liu Z, Wang J, et al. Comprehensive characterisation of compartment-specific long non-coding RNAs associated with pancreatic ductal adenocarcinoma. Gut 2019;68:499–511. [PubMed: 29440233]
59. Price ND, Magis AT, Earls JC, et al. A wellness study of 108 individuals using personal, dense, dynamic data clouds. Nat Biotechnol 2017;35: 747–756. [PubMed: 28714965]
60. Zubair N, Conomos MP, Hood L, et al. Genetic predisposition impacts clinical changes in a lifestyle coaching program. Sci Rep 2019;9:6805. [PubMed: 31048771]
61. Dinalankara W, Ke Q, Xu Y, et al. Digitizing omics profiles by divergence from a baseline. Proc Natl Acad Sci U S A 2018;115:4545–4552. [PubMed: 29666255]
62. Eddy JA, Hood L, Price ND, et al. Identifying tightly regulated and variably expressed networks by Differential Rank Conservation (DIRAC). PLoS Comput Biol 2010;6:e1000792. [PubMed: 20523739]

63. Yurkovich JT, Hood L. Blood is a window into health and disease. Clin Chem 2019;65:1204–1306. [PubMed: 31171530]